REMARKS

Claims 1-16, 18 to 27, 29 to 44 and 46 to 49 stand rejected and are currently pending. By the present communication, claims 47-49 has been canceled subject to Applicant's right to pursue these claims in a continuation application. No new matter is introduced by the subject amendments.

Regarding the Rejections Under 35 U.S.C. § 112, First Paragraph

The rejection of claims 1 to 16, 18 to 27, 29 to 44 and 46 to 49 under 35 U.S.C. § 112, first paragraph, as allegedly lacking an enabling disclosure for the full scope of the claimed invention is respectfully traversed. Applicant respectfully disagrees with the Examiner's assertion, at page 4, lines 7-8, that:

> The claims recite methods of detection of an increase in any and all BAG gene expressions as an indicator of decreased risk of metastasis or recurrence for any and all cancer.

Regarding claims 16, 19-27, 29-37 and 44, because these claims explicitly require that the cancer is breast cancer, claims 16, 19-27, 29-37 and 44 do not recite a decreased risk of metastasis or recurrence for **any and all cancer**. Regarding the detection of the BAG gene expression level, as set forth in our previous response, the anti-BAG-1 antibody used in Applicant's Examples recognizes all three isoforms of BAG-1. Thus, it is respectfully

submitted that those of skill in the art, in view of Applicant's specification, would reasonably expect that detection of an increase in one or more of the three human BAG-1 isoforms exemplified in the specification, would be indicative of reduced risk of tumor metastasis and recurrence.

Applicant respectfully disagrees with the Examiner's assertion that the art describes correlations of increased BAG expression with poorer prognosis, increased recurrence and increased metastasis, contradicting the claimed invention. In regard to the cited references that allegedly contradict the present invention, Applicant submits that the cited references do not accurately reflect the correlation between BAG-1 levels and prognosis, recurrence, or metastasis. Specifically, the Tang et al. reference describes a retrospective study of breast cancer patients using immunohistochemical staining of paraffin-embedded breast tumor tissues. However, unlike the work described in the specification which underlies the present invention, which used a monoclonal antibody for BAG-1 detection, Tang et al. used a polyclonal antibody. Polyclonal antibodies exhibit a lowered specificity compared to monoclonal antibodies, and the use of a polyclonal antibody may result in non-specific signals leading to erroneous detection of BAG-1 levels. In addition, the patient populations surveyed by Tang et al. were very heterogenous with heterogeneous treatments, making the statistical analysis highly prone to bias. For example, Table 1 in Tang et al. (page 1712) shows that patients were selected at all stages of disease (Stages I to IV) and that 22 patient samples had no associated staging information. Also, 54 patients received single modality

radiation therapy, chemotherapy, or hormonal therapy, 18 patients received no therapy, and 29 patients received a combined-modality treatment. In contrast, Applicant of the present invention used a well-defined cohort of patients, who received uniform treatment. For example, and as opposed to the Tang et al. study, all 116 patients were in early stage disease (Stage I and II). In addition, all 116 patients were treated with lumpectomy followed by radiation therapy. There were 17/116 (15%) patients treated with adjuvant systemic chemotherapy and 20/116 (17%) patients treated with tamoxifen therapy (page 32, lines 11-20). Therefore, the treatment population studied in the Example was more homogeneous than in Tang et al. Accordingly, Applicant submits that the difference in experimental methods between Tang et al. and the present invention is substantial and that the experimental design described in Tang et al. was flawed. Therefore, the results of Tang et al. do not accurately reflect the correlation of BAG expression with prognosis of disease free or overall survival in a cancer patient.

Applicant submits that the Zapata et al. reference does not present a correlation between BAG-1 levels and prognosis, recurrence, or metastasis. The Office Action refers to page 138, first column, third paragraph which states:

> This report provides the first evidence of BAG-1 expression in breast cancers. Interestingly, the intensity of BAG-1 immunostaining was often higher in invasive cancers compared to normal epithelium.

This conclusion was based on immunohistochemical analysis of twenty breast cancer biopsy specimens (page 136, first column, second paragraph). However, in analyzing the results of this study the authors state at page 137, first paragraph:

> Finally, the intensity of BAG-1 was significantly higher among carcinoma in situ than normal epithelium ($p=0.01$) but <u>not</u> in invasive cancer. (Emphasis added)

Therefore, the relationship between increased BAG-1 levels and invasive cancer was not significant.

In regard to the conclusion that BAG-1 was higher among carcinomas, Zapata et al. caution that no quantitative relations between normal and malignant breast tissue should be inferred since paired samples of tumor and adjacent tissue were not employed, the tissue specimens were heterogeneous in cell type and the relative levels of some Bcl-2 family proteins may fluctuate with estrous cycle (paragraph bridging pages 135-136). Therefore, these results described by Zapata et al. do not teach that BAG-1 levels are higher in invasive breast cancers. Moreover, in this reference, the breast cancer biopsy specimens tested were presented with no associated patient staging or treatment information, and thus may be heterogeneous as in the case of Tang et al. as discussed above. Therefore, the results of Zapata et al. do not accurately reflect the correlation of BAG expression with prognosis of disease free or overall survival in a cancer patient.

Applicant respectfully submits that because Yawata et al. and Takaoka et al. are related to human gastric carcinoma and murine melanoma, respectively, these references are not relevant to claims 16, 19-27, 29-37 and 44, which are directed to breast cancer.

Claims 1-15, 38-43 and 46 are directed to methods and kits for determining a prognosis of disease free or overall survival in a patient suffering from cancer by determining a BAG gene expression level in a cancerous tissue sample or body fluid from said patient and classifying said patient as belonging to either a first or second group of patients, wherein said first group of patients having high levels of expression of the BAG gene is classified as **having a different likelihood** of suffering tumor recurrence or spread than said second group of patients having low levels of expression of the BAG gene. Applicant's specification provides an example of increased BAG expression levels as correlating with a decreased risk of breast tumor recurrence or spread. In addition, the previously submitted Rule 132 Declaration of Dr. Reed provides data related increased BAG expression levels correlating with an increased risk of prostate tumor recurrence or spread. Thus, for a given cancer, it is respectfully submitted that those of skill in the art, in view of Applicant's specification could determine using routine experimentation whether two different groups of BAG expression levels exist, and whether one of these groups has a different likelihood of tumor recurrence or spread than the other group.

Applicant respectfully submits that because claims 16, 19-27, 29-37 and 44 require that the cancer is breast cancer, the Examiner's concern related to the description in the previous Rule 132 Declaration of the correlation between increased levels of BAG expression and unfavorable prognosis for prostate cancer is only relevant to claims 1-15, 38-43 and 46-49, which do not explicitly require breast cancer. Applicant respectfully disagrees with the Examiner's assertion, at p. 6, line 4 of the Official Action, that:

> The disclosure fails to teach this association, or to address the relationship of BAG levels to prostate cancer at all.

Applicant's specification, at page 7, lines 1-10, teaches that:

> The invention methods are useful in the prognosis of disease-free or overall survival of individuals with neoplastic diseases, including both solid tumors and hematopoietic cancers. Exemplary neoplastic diseases include carcinomas, such as adenocarcinomas and melanomas; and sarcomas, such as various leukemias or lymphomas. Of particular interest are breast cancer, <u>prostate cancer</u>, lung cancer, colon cancer, leukemia, lymphoma, and oral cancer; more particularly breast cancer. (emphasis added).

Moreover, the specification, at page 11, lines 5-11, explicitly teaches that BAG expression has been found to be present at abnormal levels in numerous cancers, including for example: colon cancer, leukemia, lymphoma, breast cancer, <u>prostate cancer</u>, lung cancer, melanoma, ovarian cancer, cervical cancer, and renal cancer (page 11, lines 5-11; emphasis added). It is respectfully

submitted that, in view of Applicant's specification, those of skill in the art, at the time of the invention, would have reasonably expected that one could routinely measure BAG levels in a patient with prostate cancer, and routinely classify said patient as belonging to a group of patients with high or low BAG expression levels. Thus, Applicant respectfully submits that Applicant's specification enables the methods and kits of claims 1-15, 38-43 and 46-49 for determining a prognosis of disease free or overall survival in a patient suffering from cancer by determining a BAG gene expression level in a cancerous tissue sample or body fluid from said patient and classifying said patient as belonging to either a first or second group of patients, wherein said first group of patients having high levels of expression of the BAG gene is classified as having a different likelihood of suffering tumor recurrence or spread than said second group of patients having low levels of expression of the BAG gene, is enabled by the specification. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of claim 23

The rejection of claim 23 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not properly described in the specification in such a way as to enable one skilled in the art to make and/or use the invention, is respectfully traversed. The Office Action alleges that there is no guidance that *in vitro* reference levels allow relative determination of BAG expression in cells. Applicant submits that

BAG expression levels have been reliably profiled in several cultured cell lines allowing one skilled in the art to readily select a cell line from those tested to obtain an appropriate reference level of BAG expression. For example, Takayama et al., Cancer Res., **58**:3116-3131 (1998; copy previously submitted with PTO Form 1449), at Table II, teach that BAG-1 protein expression levels (in ng per 50 µg total protein) were determined using immunoblot analysis for 67 human tumor cell lines including the National Cancer Institute screening panel of 60 human tumor cell lines, as well as an additional five human prostate cancer cell lines. It is respectfully submitted that, in view of Applicant's specification, one skilled could have selected an *in vitro* cultured cell line representative of a tumorigenic or non-tumorigenic state that expresses BAG at a particular level, such that a reference level of BAG expression could routinely be determined for use in the invention methods. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejection of claim 47

The rejection of claim 47 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not properly described in the specification has been rendered moot by the cancellation of claim 47 herein, subject to Applicant's right to file a continuation application thereon.

Rejection of claims 48 and 49

The rejection of claims 48 and 49 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not properly described in the specification has been rendered moot by the cancellation of claims 48 and 49 herein, subject to Applicant's right to file a continuation application thereon.

Regarding the Rejection under 35 U.S.C. 102(b)

The rejection of claims 1, 3 to 4, 6 to 11, 13 to 15, 42, 43, 45 and 46 as allegedly anticipated under 35 U.S.C. §102(b) by Zapata et al. is respectfully traversed. Applicant note that claim 45 was previously cancelled. The Office Action alleges that Zapata et al. describe a statistically significant correlation between BAG-1 immunostaining and invasive cancer, which is known to have a poorer prognosis.

Applicant's invention as defined by claim 1 and its dependents distinguishes over the Zapata reference by requiring a method for determining a prognosis of disease free or overall survival in a patient suffering from cancer, said method comprising:

(a) determining a BAG gene expression level in a cancerous tissue sample or body fluid from said patient; and

(b) classifying said patient as belonging to either a first or second group of patients, wherein said first group

of patients having high levels of expression of the BAG gene is classified as having a different likelihood of suffering tumor recurrence or spread than said second group of patients having low levels of expression of the BAG gene.

In contrast, there is no teaching by Zapata et al. that levels of BAG could be used to determine a prognosis of disease-free or overall survival in a patient suffering from cancer as required in the method claims. In addition, there is no description in the reference of classifying a group of cancer patients having high levels of BAG as having a different likelihood of tumor recurrence or spread than a second group having low levels of BAG. For example, Zapata et al. state that the multitude of apoptosis-regulating proteins expressed in these tumor cells and the complex interactions among these proteins suggest that the relative resistance to apoptosis in individual cases of breast cancer will be difficult to predict (page 137, first paragraph in Discussion). Therefore, because Zapata et al. actually teaches away from seeking a correlation between BAG levels and prognosis of disease free or overall survival in a cancer patient, Zapata et al. does not teach classifying a group of cancer patients having high levels of BAG as having a different likelihood of tumor recurrence or spread than a second group having low levels of BAG, as required by Applicant's claims. Thus, Zapata et al. does not anticipate Applicant's claims. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Regarding the Rejection under 35 U.S.C. 103(a)

The rejection of claims 1, 3, 4, 6 to 11, 38 to 43 and 45 to 46 as allegedly obvious under 35 U.S.C. §103(a) over Zapata et al. in view of Sano et al. respectfully is traversed. Applicant note that claim 45 was cancelled in the previous response. As set forth above, Zapata et al. actually teaches away from seeking a correlation between BAG levels and prognosis of disease free or overall survival in a cancer patient; and does not teach classifying a group of cancer patients having high levels of BAG as having a different likelihood of tumor recurrence or spread than a second group having low levels of BAG, as required by Applicant's claims.

The secondary reference Sano et al. is unable to cure the deficiencies of the primary Zapata reference because it merely teaches immuno-PCR detection techniques. It is respectfully submitted that because the results described by Zapata were uncertain and preliminary, and because Sano et al. is merely related to immuno-PCR detection technuiques, one of ordinary skill in the art would not have been motivated to combine Sano et al. with Zapata et al. Moreover, the combination of Zapata and Sano does not teach or suggest Applicant's claimed methods of determining BAG-1 protein expression levels for determining a prognosis of disease free or overall survival in a patient suffering from cancer. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

Respectfully submitted,

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